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Effect of Certain Drugs in Perfused Human Placenta XII: Autacoid Antagonism by Phenothiazines

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Abstract □ The effects of chlorpromazine, prochlorperazine, and trifluoperazine on the pressor actions of serotonin, angiotensin, and bradykinin in the perfused vessels of full-term human placentas were investigated. A significant inhibition of the effect of serotonin was observed with trifluoperazine and chlorpromazine but not with prochlorperazine. This inhibition is attributed to the ability of phenothiazines to cause adrenergic blockade. Because both bradykinin and angiotensin could not be consistently antagonized, it is concluded that they must act primarily *via* musculotropic mechanisms and only secondarily by stimulation of adrenergic receptors.

Keyphrases □ Chlorpromazine—effects on pressor actions of serotonin, angiotensin, and bradykinin in perfused human placenta □ Prochlorperazine—effects on pressor actions of serotonin, angiotensin, and bradykinin in perfused human placenta □ Trifluoperazine—effects on pressor actions of serotonin, angiotensin, and bradykinin in perfused human placenta □ Serotonin—pressor actions in perfused human placenta, effects of chlorpromazine, prochlorperazine, and trifluoperazine □ Angiotensin—pressor actions in perfused human placenta, effects of chlorpromazine, prochlorperazine, and trifluoperazine □ Bradykinin—pressor actions in perfused human placenta, effects of chlorpromazine, prochlorperazine, and trifluoperazine □ Autacoid antagonism—effects of chlorpromazine, prochlorperazine, and trifluoperazine on pressor actions of serotonin, angiotensin, and bradykinin in perfused human placenta □ Phenothiazines—chlorpromazine, prochlorperazine, and trifluoperazine, effects on pressor actions of serotonin, angiotensin, and bradykinin in perfused human placenta

It is well established that the endogenous autacoids serotonin, angiotensin, and bradykinin are present and that their levels fluctuate in human placental and/or related tissues (1–8). Several investigations linked high blood levels of angiotensin (9), renin (10), and serotonin (11) to the pathogenesis of the toxemias of pregnancy. Increased pressor response to angiotensin was observed in preeclamptic women (9); increased renin levels were reported in eclamptic and preeclamptic women (12), and decreased angiotensinase levels were found in toxemic women (13).

Serotonin, angiotensin, and bradykinin share two noticeable actions on the perfused placental vasculature: vasoconstriction with an associated increase in blood vessel pressure and increased blood vessel permeability (14–20). They also share similarities in their mechanisms of action in that they all cause α-receptor stimulation in these vessels (16, 20). Serotonin and angiotensin cause direct vascular smooth muscle stimulation, while bradykinin causes release of norepinephrine from unspecified storage sites in the placenta.

Chlorpromazine antagonizes the vasoconstrictor action of serotonin in the perfused human placental blood vessels by approximately 67.8% (21). Chlorpromazine also inhibits the ability of serotonin to cause intrauterine deaths (22). In addition, chlorpromazine and other phenothiazines block the increased vascular permeability of serotonin injections in the hindpaw of rats (23).

The phenothiazines are presently prescribed for anxiety states, tranquilization, motion sickness, night sedation, and preanesthetic medication. They are used as analgesics in labor and to prevent nausea and vomiting during labor and morning sickness (24). These compounds have strong adrenergic blocking activity and weaker cholinergic blocking activity, and they can block the actions of serotonin both *in vivo* and *in vitro* (25). The phenothiazines and the previously mentioned autacoids are capable of crossing the "placental barrier," since their molecular weight is less than 1000. Furthermore, the phenothiazines are suspected of con-

tributing to hyperbilirubinemia in the premature infant (26) and to respiratory depression either singly or by potentiating narcotic analgesics or the gaseous anesthetics (27, 28). They are rapidly absorbed (29), and metabolites, as well as free chlorpromazine, have been detected in the urine of patients 6–18 months after discontinuation of a therapeutic regimen (30).

Since the phenothiazines are prescribed during pregnancy and data on the antagonism of only one autacoid—serotonin—by a phenothiazine are available, the purpose of this investigation was to determine in the placental vasculature the possible antagonistic efficacy of several phenothiazines on serotonin and other autacoids that may be exerting toxic effects during some pregnancies. Possibly an assessment can then be made on the benefits of phenothiazine usage during normal as well as complicated pregnancies.

EXPERIMENTAL

Normal human placentas delivered at term were used. They were obtained no more than 20 min after parturition and were transported to the laboratory in an insulated container filled with Tyrode's solution preheated to 38°. Each placenta was then placed in a stainless steel tray filled with Tyrode's solution, and the attached membranes were dissected free. The umbilical cord was also shortened at this time to approximately 4 cm. A preheated 2.3% sodium citrate solution was perfused through the umbilical vein and one umbilical artery to remove clots and to flush the vessels free of blood.

The cannulation procedure, the methods of recording and maintaining flow and perfusion pressure, and the instrumentation were described previously (31, 32). With 40 successful placental preparations, each lasting 2–4 hr, 59 experiments were performed.

The experimental regimen was divided into four consecutive steps. After a stable baseline pressure was established, the autacoid agonist to be tested was administered as the control response. The second drug to be administered was the antagonist (a phenothiazine), usually at a 15-min interval from the first injection. The agonist was then readministered at a 5–10-min interval after the phenothiazine. Finally, another injection of agonist was made 15 min later.

The doses of the agonists, serotonin, angiotensin, and bradykinin, were all 50 μg of drug in a volume of 0.5 ml. This dose was shown previously to produce an easily observable rise in vessel pressure for all three agonists (20, 33, 34). The doses of the antagonists, chlorpromazine hydrochloride, trifluoperazine hydrochloride, and prochlorperazine edisylate, were all 1 mg. Again, this dose was based on previous work showing effective serotonin antagonism at this range (21). The mean pressure change at maximal antagonism of the pressor effect of the agonist as compared to control was the basis for comparing the antagonistic abilities of the phenothiazines. Determination of the significance of an antagonistic action to the autacoids was calculated using the paired Student *t* test, with a probability value of 0.05 being significant (35).

The following drugs were administered to the placental circulation *via* the cannula entering the arterial side of the perfused placenta: serotonin creatinine sulfate[1], 0.01%; angiotensin amide[2], 0.01%; bradykinin triacetate[3], 0.01%; chlorpromazine hydrochloride[4], 0.1%; prochlorperazine edisylate[5], 0.5%; and trifluoperazine hydrochloride[6], 0.2%.

RESULTS

The following results, summarized in Tables I–III, were obtained on the full-term human placental vessels perfused at pressures of 70–100 mm Hg. The corresponding flow rate into the vasculature ranged between 41 and 62 ml of Tyrode's solution (modified with 0.525% povidone)/min.

Table I—Comparison of the Effect of Chlorpromazine (1 mg) on Three Autacoids[a]

Autacoid[b]	Mean Change in Pressure, mm Hg	*SE*[c]	*p* Value[d]
Serotonin	−16	±7.3	<0.05
Bradykinin	−4	±7.3	<0.35
Angiotensin	−1	±2.6	<0.45

[a] Six experiments. [b] Dose of 50 μg. [c] Standard error of the difference. [d] The *p* value was calculated from a paired *t* test; a *p* value of <0.05 was significant.

Effects of Chlorpromazine on Autacoids—*Serotonin*—Serotonin in a 50-μg dose was a consistently good constrictor of placental vessels, with initial pressure increases of 6–50 mm Hg. After a 1-mg dose of chlorpromazine and a 25-min interval, the action of serotonin was markedly inhibited in five of the six experiments. The mean pressure change for the six experiments was −16 mm Hg, corresponding to a percent change of −45%.

Bradykinin—A 50-μg dose of bradykinin also gave consistent pressor responses. In the six experiments, bradykinin showed an initial range of 3–43 mm Hg. Subsequent to 1 mg of chlorpromazine at 25 min, there were percent changes of from −91 to 79%. In only two experiments was bradykinin antagonized. The mean percent pressure change was 22%.

Angiotensin—The initial responses to a 50-μg dose of angiotensin in the placental vessels ranged from 6 to 25 mm Hg. The pressure changes after 1 mg of chlorpromazine were divided equally, with three experiments showing increases and three showing decreases, with a total mean percent change of 27%.

Effects of Prochlorperazine on Autacoids—*Serotonin*—The initial pressor responses to a 50-μg dose in these six experiments ranged from 7 to 23 mm Hg. A 1-mg dose was chosen to determine the effect of prochlorperazine on the pressor actions of the autacoids. Twenty-five minutes after this dose, the percent pressure changes from a dose of serotonin ranged from −59 to 147% with a mean of 38%. Four preparations demonstrated augmented responses, while only two showed antagonism with prochlorperazine.

Bradykinin—Bradykinin at the same dose showed initial pressor responses of 6–29 mm Hg in the six preparations tested. With 1 mg of prochlorperazine and a 25-min lapse, bradykinin produced percent changes of from −31 to 59%. The resulting mean percent change was −4%.

Angiotensin—In six experiments using a 50-μg dose of agonist and a 1-mg dose of antagonist, there were responses of 4–15 mm Hg before the agonist and 5–18 mm Hg after the antagonist. The mean percent change was 7%, with three experiments showing augmentation and three showing decreased responses.

Effects of Trifluoperazine on Autacoids—*Serotonin*—The same doses of both agonist and antagonist were chosen for this series. The initial pressure increases with agonist were 4–32 mm Hg. After the 25-min interval, the pressor responses dropped to a range of 3–15 mm Hg. The mean percent change was a decrease of 6%.

Bradykinin—The initial responses to 50 μg ranged from 3 to 51 mm Hg. The mean percent change after the antagonist (1 mg) and 25 min was a 22% increase, although four of these preparations demonstrated an inhibitory action.

Table II—Comparison of the Effect of Prochlorperazine (1 mg) on Three Autacoids[a]

Autacoid[b]	Mean Change in Pressure, mm Hg	*SE*[c]	*p* Value[d]
Serotonin	1	±4.5	<0.45
Bradykinin	−2	±1.3	<0.15
Angiotensin	0	±0.6	<0.50

[a] Six experiments. [b] Dose of 50 μg. [c] Standard error of the difference. [d] The *p* value was calculated from a paired *t* test; a *p* value of <0.05 was significant.

[1] Aldrich Chemical Co., Milwaukee, Wis.
[2] Hypertensin, valyl-5-angiotensin II amide, Lot B-5578, supplied through the courtesy of Ciba Pharmaceutical Co., Summit, N.J.
[3] Nutritional Biochemicals Corp., Cleveland, Ohio.
[4] Thorazine, Smith Kline and French Laboratories, Philadelphia, Pa.
[5] Compazine, Smith Kline and French Laboratories, Philadelphia, Pa.
[6] Stelazine, Smith Kline and French Laboratories, Philadelphia, Pa.

Table III—Comparison of the Effect of Trifluoperazine (1 mg) on Three Autacoids[a]

Autacoid[b]	Mean Change in Pressure, mm Hg	SE[c]	p Value[d]
Serotonin	−6	±2.8	<0.05
Bradykinin	−9	±6.6	<0.15
Angiotensin	−1	±1.6	<0.20

[a] Six experiments. [b] Dose of 50 μg. [c] Standard error of the difference. [d] The p value was calculated from a paired t test; a p value of <0.05 was significant.

Angiotensin—A 50-μg dose of angiotensin in seven experiments demonstrated initial pressure increases of 7–20 mm Hg. Subsequent to the 1-mg dose of trifluoperazine, the change in pressure from control ranged from −10 to 2 mm Hg, with a mean percent change of −5%.

When tested alone, the phenothiazines showed slight vasodilator capabilities that were transient and the pressure rapidly returned to baseline.

DISCUSSION

Chlorpromazine had a significant inhibitory effect on the pressor action of serotonin. This result reinforces the conclusion that chlorpromazine is a potent antagonist to serotonin in the human placental blood vessels (21). At the same dose level as chlorpromazine, trifluoperazine also demonstrated powerful antagonism to the pressor action of serotonin, while prochlorperazine exhibited little ability in this direction.

Serotonin causes constriction in the perfused human blood vessels primarily *via* α-adrenergic stimulation and, secondarily, by a direct stimulation of the vascular smooth muscle (16). Since the phenothiazines have a strong adrenergic blocking action (25), it can be concluded that the major inhibition by both chlorpromazine and trifluoperazine is mediated by a blockade at the α-receptors in the placental vessels; at no time was the direct muscular action of serotonin abolished by these compounds. The lack of an inhibitory action with prochlorperazine suggests that it has less α-blocking activity than the other phenothiazines in this preparation.

Via the use of negative musculotropic agents, α-blockers, and β-blockers, it was determined that angiotensin exerts its vasopressor action primarily by direct muscular stimulation, secondarily by α-receptor stimulation, and possibly by a third component of β-receptor stimulation that offsets the other two effects (36). The effect of chlorpromazine on the pressor response to angiotensin was practically negligible, as was that with prochlorperazine. Theoretically, since the α-adrenergic component of angiotensin is blocked, one would expect a greater degree of inhibition. But since the opposing β-stimulation is also blocked by the phenothiazines, responses close to the initial values were observed. Trifluoperazine showed the greatest inhibitory potential, possibly due to a greater direct muscular depressant action.

The 1-mg dose of chlorpromazine did not yield consistent inhibitory effects on the vasopressor action of bradykinin. The responses to bradykinin after prochlorperazine and trifluoperazine were diminished slightly but not enough to be statistically significant. The mechanism of action of bradykinin on vascular beds has not, as yet, been clearly defined. Previous experiments (20) showed that its action is mechanistically unlike the actions of serotonin, acetylcholine, or histamine. It has been stated that the action of bradykinin on extravascular smooth muscle is directly mediated (37), and studies on the rat uterus (38), guinea pig intestine (38), and human umbilical arteries (19) also gave evidence of a direct positive musculotropic action with bradykinin. Therefore, it can be assumed that bradykinin's vasoconstrictor action in the perfused placental vessels is also due largely to a direct action.

One possible mode of action shared by these three autacoids is that they are all capable of releasing catecholamines. Angiotensin by itself releases catecholamines from the nerve endings in certain tissues (39), while each of the three releases catecholamines from the adrenal glands (40–42). Bucknum (43) pursued this direction by pretreatment of the placental preparation with reserpine and concluded that norepinephrine release could possibly comprise a part of the pressor activity of serotonin. This fact may be supported by the present study, in which prior administration of a phenothiazine blocked the α- and β-receptors to any norepinephrine released by serotonin. Consequently, one should expect a diminished response, which was the case for two of the three antagonists.

Bucknum (43) also found, with the same pretreatment, that angiotensin may also exert its action partially through norepinephrine release. But this hypothesis is not further solidified by the present results, since little antagonism to angiotensin by the phenothiazines was observed. Prior to that study, it had been determined that bradykinin releases norepinephrine from unspecified storage sites in the placenta (20). This finding presents the possibility of a minor α-receptor-stimulating component in bradykinin's pressor activity. The present experiments do not entirely rule out this possibility, since a diminution of the action of bradykinin, although not significant, was observed with two of the three phenothiazines.

Considerable evidence is on hand to implicate at least two of these autacoids, serotonin and angiotensin, as being partially responsible for, or contributing to, the complications arising in pregnancy. Placental infarctions are more frequent in pregnancies complicated with essential hypertension, toxemias of pregnancy, chronic nephritis, lupus erythematosus disseminata, and diabetic microangiopathy (44, 45). Marais (46) found significant correlation between clinical hypertension, especially with proteinuria, and decidual arteriolar disease, placental infarction, and premature separation of the placenta. Fetal renin also may be involved in the elevated blood pressure in the toxemias of pregnancy (47), and the ratio of the concentrations of renin in the umbilical artery over the umbilical vein was found to be highest in infants suffering respiratory distress (48).

Monoamine oxidase activity is also decreased in the placentas of toxemic patients, suggesting that serotonin may accumulate (49) and may lead to vasospasm and local placental anoxia. This finding is supported by a report of serotonin increase in placentas from toxemic patients (50). There is also a local excess of L-aromatic amino acid decarboxylase, an enzyme that synthesizes most of the important amines including serotonin (49). Bradykinin has not been found in excess amounts during complicated pregnancies, but one can easily see that, because of its vasoconstrictive effect, it may be another underlying toxic agent.

It can be suggested that if the phenothiazines are administered, they could perhaps serve the dual purpose during labor of producing sedation and diminishing the effects of autacoid toxicity in both mother and fetus. Consequently, phenothiazine usage as part of the therapeutic regimen in normal pregnancies and in those that manifest toxic symptoms should be tested clinically, although the usage should be limited to after the first trimester.

SUMMARY AND CONCLUSIONS

1. Chlorpromazine and trifluoperazine were potent antagonists to the pressor responses of serotonin in the perfused human placental vessels, while prochlorperazine was not.

2. Chlorpromazine, trifluoperazine, and prochlorperazine did not demonstrate significant antagonism to the effect of both angiotensin and bradykinin in these same vessels.

3. A possible component to the vasopressor action of serotonin is suggested to be the release of norepinephrine.

4. The primary site where the inhibition of serotonin by the phenothiazines is manifested is presumed to be at the adrenergic receptors, with only a slight possibility of direct negative musculotropic action.

5. From the degree of efficacy of antagonism in the placental vessels, it is concluded that trifluoperazine is the most potent antagonist followed by chlorpromazine. Prochlorperazine is inactive.

6. It is suggested that phenothiazine usage be tested clinically in both complicated and normal pregnancies, especially at term.

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